Efficacy and Safety of the Once-Weekly GLP-1 Receptor Agonist Albiglutide Versus Sitagliptin in Patients With Type 2 Diabetes and Renal Impairment: A Randomized Phase III Study

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OBJECTIVE
To evaluate weekly subcutaneous albiglutide versus daily sitagliptin in renally impaired patients with type 2 diabetes and inadequately controlled glycemia on a regimen of diet and exercise and/or oral antihyperglycemic medications.

RESEARCH DESIGN AND METHODS
In this Phase III, randomized, double-blind, multicenter, 52-week study, the primary study end point was HbA1c change from baseline at week 26 in patients with renal impairment, as assessed with estimated glomerular filtration rate and categorized as mild, moderate, or severe (≥60 to ≤89, ≥30 to ≤59, and ≥15 to ≤29 mL/min/1.73 m², respectively). Secondary end points included fasting plasma glucose (FPG), weight, achievement of treatment targets, hyperglycemic rescue, and safety.

RESULTS
Baseline demographics were similar across treatment and renal impairment groups with overall mean age of 63.3 years, BMI of 30.4 kg/m², HbA1c of 8.2% (66 mmol/mol), and diabetes disease duration of 11.2 years. HbA1c change from baseline at week 26 was significantly greater for albiglutide than sitagliptin (−0.83% vs. −0.52%, P = 0.0003). Decreases in HbA1c, FPG, and weight were seen through week 52. Time to hyperglycemic rescue through week 52 was significantly longer for albiglutide than sitagliptin (P = 0.0017). Results of safety assessments were similar between groups, and most adverse events (AEs) were mild or moderate. The incidences of gastrointestinal AEs for albiglutide and sitagliptin were as follows: overall, 31.7%, 25.2%; diarrhea, 10%, 6.5%; nausea, 4.8%, 3.3%; and vomiting, 1.6%, 1.2%, respectively.

CONCLUSIONS
Once-weekly albiglutide therapy in renally impaired patients with type 2 diabetes provided statistically superior glycemic improvement with almost similar tolerability compared with daily sitagliptin therapy.
The steady rise in the prevalence of type 2 diabetes worldwide has become a major health care issue due to associated increases in patient morbidity and mortality secondary to cardiovascular, renal, and neurological disease complications and the rising monetary and resource costs needed to manage these complications. Renal insufficiency is a common comorbidity in patients with type 2 diabetes, and the prevalence of chronic kidney disease (CKD) in patients with type 2 diabetes has been increasing (1), with the reported overall incidence of renal impairment in patients with type 2 diabetes ranging from 15 to 35% [based on estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²] (2–4).

Current treatment options for glycemic control are significantly limited for patients with type 2 diabetes and CKD (5,8–11), which often leads to the introduction of sulfonylurea and insulin therapy to maintain glycemic control. Further, therapeutic options for glycemic control can be associated with significant risks of hypoglycemia, weight gain, and fluid retention, which may add to the complexity of maintaining blood glucose, body weight, and blood pressure in this population (12–15).

Albiglutide, a novel, long-acting glucagon-like peptide-1 receptor (GLP-1R) agonist, was designed to retain the therapeutic actions of GLP-1 while having a greatly extended duration of action. Albiglutide was synthesized through genetic modification that resulted in the attachment of two modified recombiant human GLP-1 fragments linked in tandem to the amino terminus of the coding sequence for human albumin, and it retains GLP-1 glucose-dependent insulinotropic activities both in vitro and in vivo (16). With a half-life of approximately 5 days, the pharmacokinetic profile of albiglutide allow for once-weekly subcutaneous injections (16–20). To date, reported clinical studies, including a phase I study in patients with varying degrees of renal impairment (GLP108370), have shown albiglutide to be an effective, safe, and tolerable therapy when administered to patients with type 2 diabetes (16–21).

This study was conducted to compare the efficacy, safety, and tolerability of albiglutide given subcutaneously once weekly with sitagliptin given orally daily in patients with type 2 diabetes and renal impairment whose glycemia was inadequately controlled on their current regimen of either diet and exercise or specific antihyperglycemic therapy. RESEARCH DESIGN AND METHODS Study Design

This phase III, randomized, double-blind, active-controlled, two parallel-group, multicenter, 52-week study (Harmony 8) (GSK study number GLP114130) compared the efficacy and safety of once-weekly subcutaneous injections of albiglutide with that of daily oral sitagliptin in renally impaired patients with type 2 diabetes. Renal impairment was defined as mild (eGFR ≥60 to ≤89 mL/min/1.73 m²), moderate (eGFR ≥30 to ≤59 mL/min/1.73 m²), or severe (eGFR ≥15 to ≤29 mL/min/1.73 m²) based on the MDRD formula (22). Albiglutide (30 mg) was given subcutaneously once weekly (with treatment-masked uptitration, if needed, to 50 mg weekly), and sitagliptin was dosed based on the eGFR value at randomization per the sitagliptin package insert. All patients continued to receive their prescribed oral antihyperglycemic medications (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications) for the duration of the study with the exception of patients with GFR <60 mL/min/1.73 m², who were washed off their background metformin. Instructions for downtitration of sulfonylureas were also provided to avoid hypoglycemia.

There were four specific study periods: prescreening and screening (~2 weeks), run-in (4 weeks), treatment period (52 weeks, including 26 weeks of initial treatment and evaluation for primary efficacy and safety followed by an additional 26 weeks of treatment for secondary efficacy and safety assessments), and posttreatment follow-up (8 weeks). Patient assessments during the treatment period varied between weekly and quarterly. Independent, blinded adjudication and review of all suspected cardiovascular events took place over the entire treatment period. An independent, blinded pancreatitis adjudication committee reviewed all reported adverse events (AEs) of pancreatitis, serious AEs (SAEs) identified through broad and narrow SMQ searches as related to pancreatitis, and other events identified by the pharmacovigilance group as related to pancreatitis, as well as amylase and/or lipase measurements (three or more times the upper limit of normal) regardless of suspected etiology, to determine whether adjudication for pancreatitis was warranted.

After randomization, patients who experienced persistent hyperglycemia qualified, on the basis of prespecified HbA1c and/or fasting plasma glucose (FPG) values, to undergo masked dose titration followed by hyperglycemia rescue as needed (Supplementary Table 2). Given the blinded nature of the study, uptitration also occurred in the sitagliptin group, but the actual dose received did not change. Patients continued to receive study medication in a blinded fashion after rescue.

The primary end point of the study was to evaluate the efficacy of albiglutide compared with that of sitagliptin on the change in HbA1c from baseline at week 26. Secondary end points over time included HbA1c, FPG, body weight, proportion of patients who met prespecified HbA1c treatment targets, time to hyperglycemic rescue, and population pharmacokinetics of albiglutide. Pharmacokinetics are not reported here, as a population model that combined data from this and three other Phase III studies will be reported separately (23). Safety end points over time included evaluations of AEs and SAEs, safety events of special interest, clinical laboratory parameters, vital sign measurements, electrocardiogram readings, and physical examinations. Immunogenicity was also evaluated. There were no changes to the statistical plan, which was finalized before the database was frozen and treatment codes were unblinded.

This study was conducted in accordance with International Committee on Harmonisation Good Clinical Practices and the Declaration of Helsinki, and all patients provided written informed consent before they participated in this study.

Patients

Male and nonpregnant, nonlactating female patients ≥18 years of age with historical diagnoses of type 2 diabetes were enrolled. Patients were required to have baseline HbA1c between 7.0 and 10.0% (53–86 mmol/mol), BMI between 20 and
45 kg/m², fasting C-peptide level of $\geq0.8$ ng/mL (0.26 nmol/L), GFR of $\geq15$ to <90 mL/min/1.73 m², hemoglobin of $\geq10$ g/dL for male patients and $\geq9$ g/dL for female patients, and normal levels of thyroid-stimulating hormone or clinically euthyroid.

Patients with malignant disease (except squamous cell or basal cell carcinoma) were excluded from the study. Further exclusion criteria included a history of diabetic gastroparesis, current ongoing symptomatic biliary disease or history of pancreatitis, significant gastrointestinal (GI) surgery or surgeries thought to significantly affect upper GI function, recent (within predefined time scales) clinically significant cardiovascular and/or cerebrovascular disease, a history of human immunodeficiency virus infection, and acute symptomatic hepatitis B or C infection. Patients who met additional exclusion criteria, including requirements for levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, or fasting triglycerides, were also excluded.

Randomization and Blinding
Approximately 500 patients were planned to be randomly assigned in a ratio of 1:1 to receive albiglutide plus sitagliptin matching placebo or albiglutide matching placebo plus sitagliptin. Eligible patients were stratified according to severity of renal impairment (mild, moderate, or severe), prior history of myocardial infarction (yes or no), and age (<65 or $\geq65$ years of age). An interactive voice response system was used for the blinded randomization, which was based on a sequestered fixed randomization schedule. Albiglutide/matching placebo was supplied as a fixed-dose (30 or 50 mg) pen injector system, which was injected subcutaneously into the abdomen. Sitagliptin (100 mg for patients with eGFR $\geq50$–89 mL/min/1.73 m², 50 mg for those with eGFR $\geq30$ to <50 mL/min/1.73 m², and 25 mg for those with eGFR <30 mL/min/1.73 m²) and matching placebo were provided as overcoated tablets or capsules. No dose adjustments were made for degrees of renal impairment after randomization. Treatment compliance was assessed for both treatment groups through the return of unused study medication.

Sample Size and Statistical Analyses
Based on an expected treatment effect of 0% and an SD of 1.2%, the test of albiglutide versus sitagliptin had at least 91% power according to a one-sided, two-sample $t$ test and a test-wise significance level of 0.025, with 200 completed patients per treatment group for a noninferiority margin of 0.4. With the significance on the noninferiority hypothesis, the superiority hypothesis had at least 90% power to reject the null hypothesis if the actual albiglutide superiority was 0.35% with a two-sided, two-sample $t$ test and a test-wise significance level of 0.05. Allowing for as great as 20% early withdrawal, loss to glycemic follow-up, and rescue, we randomized 250 patients to each treatment group.

The primary analysis of the change in HbA₁c from baseline response at week 26 was applied to the intent-to-treat population using an ANCOVA model with main effects for treatment group, region, renal impairment severity, history of prior myocardial infarction, and age category as factors and baseline HbA₁c as a continuous covariate. Treatment-effect estimates (and associated hypothesis tests) of albiglutide were evaluated within this ANCOVA model as least squares (LS) means contrasts relative to sitagliptin. Patients who qualified for hyperglycemia rescue had their primary end point value for change in HbA₁c from baseline recorded at the time of rescue. Follow-up assessments continued beyond rescue. For patients who withdrew consent, were lost to follow-up, or otherwise discontinued participation, the last observation carried forward (LOCF) method was used for the primary analysis of HbA₁c. The ANCOVA analyses were also performed on HbA₁c change from baseline by visit up to week 52 with the observed case (OC) algorithm, which only included patients with data at the specified analysis time point and excluded data carried forward from earlier observations as was done under the LOCF procedure. For this report, LOCF analyses that excluded posthyperglycemic rescue values were used for the week 26 data and OC analyses that excluded posthyperglycemic rescue values were used for the week 52 data unless otherwise stated.

The other continuous secondary efficacy end points were analyzed in a fashion similar to that used for the primary end point. Fifty-two-week efficacy was evaluated using time to hyperglycemia rescue and the proportion of patients who received hyperglycemia rescue. The safety analyses included comparative summaries of vital sign measurements, laboratory values, physical examination assessments, electrocardiogram readings, and on-therapy AE incidence rates, with events “on therapy” defined as events that occurred within 56 days of treatment regardless of rescue.

All analyses were conducted with SAS software (SAS Institute, Cary, NC), version 9.1 or higher.

RESULTS
Patients
This study was conducted at 134 centers in 15 countries between 7 May 2010 and 30 May 2012. A total of 771 patients were assessed for eligibility, and 507 patients were randomly assigned to receive albiglutide ($n = 254$) or sitagliptin ($n = 253$) (Supplementary Fig. 1). At least 97% of patients in each group received one or more doses of study medication. Overall dropout rates by week 52 were $\sim$20% in the albiglutide group and 25% in the sitagliptin group.

Patient demographic and baseline characteristics were similar between the albiglutide and sitagliptin treatment groups. Of the assessed characteristics, only HbA₁c category showed a statistically significant difference between groups ($P < 0.05$); however, this difference was not considered to be clinically relevant and was likely due to the higher mean HbA₁c at baseline in the sitagliptin group (Table 1). Overall, $\sim$52%, 41%, and 7% of patients had mild, moderate, or severe renal impairment, respectively.

Approximately 57% of patients (141 of 249) on albiglutide required dose uptitration to 50 mg, with 35% undergoing uptitration by week 26 and an additional 22.1% by week 48. The mean albiglutide dose was 40.2 mg at week 26 and 42.4 mg at week 52. The proportion of albiglutide-treated patients who required uptitration from 30 mg weekly to 50 mg weekly was similar among the mild (53% [69 of 128 patients]), moderate (60% [61 of 102 patients]), and severe (58% [11 of 19 patients]) renal impairment subgroups.

Treatment compliance was 98% for albiglutide and 93% for sitagliptin. Compliance rates $<80$% were lower in the albiglutide (1.6%) and matching placebo
### Table 1—Patient demographics and baseline characteristics by treatment group (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Albiglutide</th>
<th>Sitagliptin</th>
<th>Total</th>
<th>P*</th>
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<tbody>
<tr>
<td>N</td>
<td>249</td>
<td>246</td>
<td>495</td>
<td></td>
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<tr>
<td>Severity of renal impairment, n (%)</td>
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<tr>
<td>Mild</td>
<td>128 (51.4)</td>
<td>128 (52.0)</td>
<td>256 (51.7)</td>
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<tr>
<td>Moderate</td>
<td>102 (41.0)</td>
<td>101 (41.1)</td>
<td>203 (41.0)</td>
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<tr>
<td>Severe</td>
<td>19 (7.6)</td>
<td>17 (6.9)</td>
<td>36 (7.3)</td>
<td></td>
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<tr>
<td>Age (years), mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>63.2 (8.37)</td>
<td>63.5 (9.02)</td>
<td>63.3 (8.69)</td>
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<td>≥65 years</td>
<td>141 (56.6)</td>
<td>138 (56.1)</td>
<td>279 (56.4)</td>
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<td>Sex, n (%)†</td>
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<tr>
<td>Female</td>
<td>113 (45.4)</td>
<td>116 (47.2)</td>
<td>229 (46.3)</td>
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<tr>
<td>Male</td>
<td>136 (54.6)</td>
<td>130 (52.8)</td>
<td>266 (53.7)</td>
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<td>Race, n (%)†</td>
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<tr>
<td>Black</td>
<td>36 (14.5)</td>
<td>42 (17.1)</td>
<td>78 (15.8)</td>
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<tr>
<td>Asian</td>
<td>84 (33.7)</td>
<td>76 (30.9)</td>
<td>160 (32.3)</td>
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<tr>
<td>White</td>
<td>113 (45.4)</td>
<td>114 (46.3)</td>
<td>227 (45.8)</td>
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</tr>
<tr>
<td>Other</td>
<td>17 (6.8)</td>
<td>16 (6.5)</td>
<td>33 (6.7)</td>
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<td>Diabetes duration (years), mean (SD)</td>
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<td></td>
<td></td>
<td>0.271</td>
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<tr>
<td></td>
<td>10.83 (7.403)</td>
<td>11.62 (7.476)</td>
<td>11.23 (7.956)</td>
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<tr>
<td>Mean Baseline HbA1c, mean (SD)</td>
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<tr>
<td>&lt;8.0% (&lt;63.9 mmol/mol)</td>
<td>8.13 (1.036)</td>
<td>8.23 (0.942)</td>
<td>8.18 (0.991)</td>
<td>0.247</td>
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<tr>
<td>≥8.0% (≥63.9 mmol/mol)</td>
<td>131 (52.6)</td>
<td>107 (43.5)</td>
<td>238 (48.1)</td>
<td>0.042</td>
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<tr>
<td>Prior myocardial infarction, n (%)</td>
<td></td>
<td></td>
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<td>0.841</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (8.4)</td>
<td>22 (8.9)</td>
<td>43 (8.7)</td>
<td></td>
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<tr>
<td>No</td>
<td>228 (91.6)</td>
<td>224 (91.1)</td>
<td>452 (91.3)</td>
<td></td>
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<tr>
<td>Body weight (kg), mean (SD)</td>
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<td></td>
<td></td>
<td>0.821</td>
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<td></td>
<td>83.25 (19.902)</td>
<td>82.84 (20.649)</td>
<td>83.04 (20.275)</td>
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<td>BMI (kg/m²), mean (SD)</td>
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<td>0.873</td>
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<td></td>
<td>30.35 (5.466)</td>
<td>30.43 (5.828)</td>
<td>30.39 (5.644)</td>
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<td>Baseline vital signs, mean (SD)</td>
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<td>Systolic blood pressure (mmHg)</td>
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<td></td>
<td></td>
<td>0.940</td>
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<tr>
<td></td>
<td>132.9 (14.78)</td>
<td>132.8 (14.94)</td>
<td>132.9 (14.87)</td>
<td></td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td>0.733</td>
</tr>
<tr>
<td></td>
<td>78.5 (10.34)</td>
<td>78.8 (9.17)</td>
<td>78.6 (9.79)</td>
<td></td>
</tr>
<tr>
<td>Baseline lipids, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.7 (1.21)</td>
<td>4.5 (1.08)</td>
<td>4.6 (1.15)</td>
<td>0.053</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.2 (0.32)</td>
<td>1.2 (0.32)</td>
<td>1.2 (0.32)</td>
<td>1.000</td>
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<td>LDL (mmol/L)</td>
<td>2.5 (0.95)</td>
<td>2.4 (0.95)</td>
<td>2.5 (0.95)</td>
<td>0.245</td>
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<td>Triglycerides (mmol/L)</td>
<td>2.3 (1.64)</td>
<td>2.0 (0.97)</td>
<td>2.2 (1.36)</td>
<td>0.014</td>
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<tr>
<td>Patients with any diabetes, n (%) condition†</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>177 (71.1)</td>
<td>172 (69.9)</td>
<td>349 (70.5)</td>
<td>0.776</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>66 (26.5)</td>
<td>61 (24.8)</td>
<td>127 (25.7)</td>
<td>0.663</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>62 (24.9)</td>
<td>58 (23.6)</td>
<td>120 (24.2)</td>
<td>0.731</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>40 (16.1)</td>
<td>49 (19.9)</td>
<td>89 (18.0)</td>
<td>0.264</td>
</tr>
</tbody>
</table>

*The P value was for testing the null hypothesis that the population values (mean or proportion) were equal between the two treatment groups (albiglutide and sitagliptin). All tests were two sided. †Patients could be counted in more than one race category. A P value was not calculated for race. ‡Diabetes conditions were not predefined in the protocol but were investigator assessed.

(1.6%) groups compared with the sitagliptin (11.4%) and matching placebo (14.8%) groups.

### Efficacy

**HbA1c Change From Baseline at Primary End Point and Over Time**

The model-adjusted LS mean for the primary end point of change from baseline in HbA1c at week 26 was −0.83% (−9.1 mmol/mol) in the albiglutide group and −0.52% (−5.7 mmol/mol) in the sitagliptin group (Fig. 1A), with similar results across all three baseline eGFR groups (data not shown). The treatment difference (albiglutide vs. sitagliptin) was −0.32% (95% CI −0.49, −0.15) (−3.5 mmol/mol [95% CI −5.4, −1.6]). The upper bound of the CI was below the prespecified noninferiority margin of 0.4% (4.4 mmol/mol), indicating noninferiority of albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin (P = 0.0003). The treatment effect of albiglutide seen at week 26 was maintained through week 52 (Supplementary Fig. 2A).

**FPG**

The change in FPG from baseline at week 26 was −1.42 mmol/L in the albiglutide group and −0.22 mmol/L in the sitagliptin group (Fig. 1B). At week 26, the difference in LS means (albiglutide vs. sitagliptin) was −1.20 mmol/L (P < 0.0001). Both treatment groups maintained decreases in FPG through week 52, with the mean change from baseline in FPG showing greater reductions for albiglutide than for sitagliptin at each time point through week 52 (Supplementary Fig. 2B). At week 52, both albiglutide and sitagliptin demonstrated sustained glycemic effects (Supplementary Fig. 28).

**Clinically Meaningful HbA1c Response**

A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of HbA1c <6.5% (<48 mmol/mol) and <7.0% (<53 mmol/mol) at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant (P = 0.0077) for the treatment target of HbA1c <7.0% (<53 mmol/mol) at week 26. The proportion of patients who reached the treatment targets of improvement in HbA1c by at least 1.0% (10.9 mmol/mol), 1.5% (16.4 mmol/mol), or 2.0% (21.9 mmol/mol) by week 26 was higher in the albiglutide group than in the sitagliptin group. The differences were not significant at week 52.

**Time to Hyperglycemia Rescue**

There was a statistically significant difference between albiglutide and sitagliptin (P = 0.0017) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs. 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs. 28.3% [68 patients]). The probability of rescue at the end of 52 weeks was 20% for albiglutide and 34% for sitagliptin. Metformin was
the most commonly used rescue medication in both treatment groups.

Change in Body Weight
Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of $-0.79$ kg for albiglutide and $-0.19$ kg for sitagliptin ($P < 0.05$). Weight loss from baseline was maintained through week 52 in the albiglutide group, whereas a small gain in mean body weight was observed in the sitagliptin group over this period ($+0.82$ kg and $0.32$ kg, respectively; $P < 0.05$ [excluding postrescue values]).

Safety
AEs
The incidence of any AE and the event rates of on-therapy AEs over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 AEs/100 person-years with sitagliptin). A summary of study AEs is presented in Table 2. Notably, there was no marked difference between the albiglutide and sitagliptin treatment groups in nausea events (4.8% vs. 3.3%) or vomiting events (1.6% vs. 1.2%) (Fig. 2). In both groups, most AEs were mild or moderate in intensity, and a similar proportion of patients in each group experienced severe AEs (13.7% with albiglutide and 14.6% with sitagliptin). On-therapy GI AEs occurred in 31.7% of albiglutide-treated patients (52.8 AEs/100 person-years) and in 25.2% of sitagliptin-treated patients (47.4 AEs/100 person-years). Diarrhea was the most commonly reported GI AE in both the albiglutide (10.0%) and sitagliptin (6.5%) groups. Other AEs prospectively defined as being of special interest included hypoglycemic events, injection-site reactions, potential systemic allergic reactions, pancreatitis, and thyroid cancer (Table 2). A higher proportion of patients in the albiglutide group (24.1%) than in the sitagliptin group (15.9%) experienced a hypoglycemic event, with fewer events occurring in patients who were not receiving sulfonylurea. One case (0.4%) of severe hypoglycemia was reported with albiglutide, and four cases (1.6%) were reported with sitagliptin. Higher proportions of patients in the albiglutide group than in the sitagliptin group (15.9%) experienced a hypoglycemic event, with few events occurring in patients who were not receiving sulfonylurea. One case (0.4%) of severe hypoglycemia was reported with albiglutide, and four cases (1.6%) were reported with sitagliptin. Higher proportions of patients in the albiglutide group than in the sitagliptin group experienced injection site reactions (8.0% vs. 3.7%, respectively) and AEs that the investigator assessed as related to study medication (21.7% vs. 13.8%, respectively). The proportion of patients who withdrew due to AEs was 10.4% in the albiglutide group and 10.6% in the sitagliptin group. Renal failure, renal impairment, and hyperglycemia were the only events that led to withdrawal reported by more than more patient in either treatment group.

SAEs
Fatal and nonfatal SAEs were similar between the albiglutide group (32 patients [12.9%]) and the sitagliptin group (36 patients [14.6%]). With the exception of atrial fibrillation (reported for four patients on albiglutide and one patient on sitagliptin), the majority of SAEs were reported for no more than two patients in each treatment group. In both groups, SAEs in the "cardiac disorders and infections and infestations" system organ class were the most commonly reported.

A total of eight deaths occurred during this study: four on albiglutide (pleural mesothelioma, pancreatic pseudocyst, sudden cardiac death, and cardiac disorder) and four on sitagliptin (ischemic stroke, subarachnoid hemorrhage, malignant melanoma, and gastroenteritis). One patient in the albiglutide group was found incidentally (on computed tomography scan during work-up of hematuria) to have two pancreatic cysts and developed pancreatitis after a pancreatic fine needle aspirate. The patient went on to develop pancreatic pseudocyst and subsequently died; the blinded adjudication committee considered the event not related to treatment.

Other Safety Parameters
Measurements of hematology, serum chemistry, vital signs, electrocardiogram readings, and physical examinations were generally unremarkable.
Albiglutide in Type 2 Diabetes Renal Impairment

Diabetes Care

Immunogenicity

The incidence of anti-albiglutide antibodies was 3.0% (7 of 231 patients) in the albiglutide group, including 1 patient (0.4%) with preexisting antibodies at baseline. All antibodies detected were of low titer and nonneutralizing. Of the seven anti-albiglutide antibody–positive patients, five tested positive for anti–human serum albumin antibodies. No reactivity with glucagon was observed. One patient in the albiglutide arm experienced a nonserious event of angioedema (local, nonsystemic, lower lip), and one patient in the sitagliptin arm experienced a serious event of angioedema (thought to be attributable to iodine). Both patients remained in the study. No SAEs or potential systemic allergic reactions were observed in the patient with anti-albiglutide antibodies.

CONCLUSIONS

This study demonstrated that once-weekly albiglutide therapy effectively and safely lowers blood glucose concentrations in patients with type 2 diabetes and varying degrees of renal impairment. The primary study end point of change from baseline in HbA1c, demonstrated the non-inferiority of albiglutide to sitagliptin. Furthermore, albiglutide was shown to be statistically superior to sitagliptin in lowering HbA1c at week 26. Nearly 60% of the patients treated with albiglutide achieved HbA1c levels <7% by week 26. However, it should be noted that more patients in the albiglutide group than in the sitagliptin group had HbA1c levels <8% at baseline. Similarly, a rapid albiglutide treatment effect was also seen with FPG, where there was a steep decline from baseline through week 4 that was maintained through week 26. These data are further supported by the sustained effect, as evidenced by the lower proportion of patients who required hyperglycemia rescue in the albiglutide group compared with the sitagliptin group.

Recent treatment guidelines have positioned incretin-based therapies, including GLP-1R agonists, as prominent therapy options due to their substantial efficacy and other positive attributes such as modest weight loss, low rates of hypoglycemia, and potential for improved cardiovascular protective actions (24). Further, these guidelines indicate that GLP-1R agonists that do not depend on renal function for clearance may be an appropriate alternative for some patients when metformin use is not an option.

With few exceptions, albiglutide and sitagliptin in this study had similar safety profiles, including for events of special interest. Although the relatively limited number of patients with severe renal impairment did experience higher frequencies of GI events compared with patients with mild and moderate renal impairment, there were no new safety concerns identified for albiglutide in this study than were included in similar previous clinical trials (16–21). Diarrhea (the most common GI event in both treatment groups) and constipation were seen at modestly higher incidences in patients treated with albiglutide than in those treated with sitagliptin; however, there was no marked difference in nausea or vomiting events in either treatment group. Furthermore, up-titration of albiglutide did not increase...
the number of reported GI events, and very few GI events led to withdrawal.

These data should be considered in the context of three unique design features in this study. First, patients with varying degrees of renal impairment were enrolled in this study. Given that many medications used to treat type 2 diabetes require dose reduction based on renal dysfunction for optimal therapeutic benefit, it is important to evaluate albiglutide in the context of this patient population. However, as a large therapeutic protein that is degraded by enzymatic catabolism to its constituent amino acids, albiglutide should not require renal elimination or any dose adjustment that is based on degree of renal impairment, as supported by a previous albiglutide study in patients with varying degrees of renal impairment (GLP108370). This unique aspect of albiglutide could prove more convenient for this challenging population, potentially improving patient medication compliance and treatment efficacy.

A second unique feature of the study design was that uptitration of the blinded study drug was need based when prespecified glycemic thresholds were met, with no preestablished or standardized time point for dose uptitration. Thus, the efficacy and safety data for albiglutide were combined for the 30-mg and 50-mg albiglutide doses. In contrast, sitagliptin dosing was determined according to each patient’s renal impairment status at baseline, as outlined in the sitagliptin prescribing information. Finally, the use of rescue medication was embedded in the treatment program to facilitate patients remaining in the study on blinded study medication through week 52, which enabled the collection of additional safety and efficacy data. While the primary efficacy assessments were independent of rescue medication, the main safety assessments included all available patient information regardless of rescue status.

This study supports the potential advantages of albiglutide treatment in patients with type 2 diabetes who have inadequate glycemic control and any degree of renal insufficiency without the need for dose adjustment.

There were several potential limitations in this study. First, there were only 19 patients with severe CKD who were treated with albiglutide (and 17 sitagliptin patients). Owing to the small sample size and the potential for variable drug responses in this population, these results for patients with severe CKD cannot be considered definitive. A second limitation was that fewer patients completed 52 weeks of treatment (198 on albiglutide and 178 on sitagliptin) than completed week 26 (220 on albiglutide and 206 on sitagliptin), which limits the interpretation of the longitudinal sustainability response. Finally, HbA1c may be a less reliable measure of efficacy in patients with renal impairment; however, both treatment groups had similar degrees of renal impairment, so the effect should not bias the interpretation of the results.

These study data from patients with CKD suggest a positive benefit-to-risk evaluation for the use of 30 or 50 mg albiglutide to reduce blood glucose levels in patients with type 2 diabetes and any degree of renal impairment, thus potentially filling a current unmet need. Results from additional phase III studies that are currently underway as part of the albiglutide clinical development program are consistent with the present efficacy and long-term safety findings from Harmony 8 (25–29).

In conclusion, albiglutide had a favorable benefit-to-risk profile and was generally well tolerated in patients with type 2 diabetes and mild, moderate, or severe renal impairment. In contrast to reports on postmarketing experience with currently approved GLP-1R agonists, albiglutide therapy was not associated with worse tolerability than that observed in other populations. In the

Figure 2—Nausea (A) and vomiting (B) through week 52 in the safety population. (A high-quality color representation of this figure is available in the online issue.)
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